If the stomach is dilated or if there is retention of food as a result of kinking in the duodenum, gastric lavage should be used as indicated. There must be a great deal of individualizing in the treatment of this condition.

THE ESTIMATION OF THE URINARY SULPHATES AND OF THE FECAL FAT IN THE DIAGNOSIS OF PANCREATIC DISEASE.

BY DAVID L. EDSALL, M.D.,
INSTRUCTOR IN CLINICAL MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA AND ASSISTANT PHYSICIAN TO THE UNIVERSITY HOSPITAL; ASSOCIATE OF THE WILLIAM PEPPER LABORATORY OF CLINICAL MEDICINE.

(From the William Pepper Laboratory of Clinical Medicine, Phœbe A. Hearst Foundation.)

A REDUCTION in the amount of ethereal sulphates in the urine has been thought to be a possible sign of pancreatic disease, for the following reasons: The production in the intestine of the substances which are finally largely excreted in the urine as so-called ethereal sulphates, is dependent upon the putrefaction of protein, and this process is due to bacterial activity. Bacteria are able to break down native albumen in only relatively small amounts, while they readily decompose comparatively large amounts of the products of proteolytic digestion. If, therefore, there were little or no proteolytic digestion going on in the intestine, as is the case in severe disease of the pancreas, the products of bacterial activity (the indol, skatol, etc.) would be largely decreased, and there would, consequently, be a reduction in the ethereal sulphates of the urine. The brief literature concerning the value of estimation of the ethereal sulphates will be reviewed after the report of two cases which are of some interest in this connection, since in both the diagnosis was ultimately made clear—by the post-mortem examination in one instance and by the subsequent clinical course in the other.

The first case occurred in a man, aged thirty-six years, who was under Dr. Stengel's care at the University Hospital. He gave a history of spasmodic attacks of colicky pain above and to the right of the umbilicus, radiating toward the left. The first attack occurred in May, 1900. The pain was subsequently felt a number of times, though the first attack was decidedly the most severe. There was an indefinite history of slight jaundice accompanying the attacks. Between the time of the first spasm of pain and his admission to the hospital in November there was a loss of about forty pounds in weight; but, excepting for the emaciation and the attacks of pain, the only symptoms had been indefinite but continuous discomfort in the epigastric region and severe constipation. Upon admission nothing could be discovered by physical examination with the exception of slight enlargement of the stomach, absence of HCl from the stomach contents, and slight stagnation of the contents.

Oppler-Boas bacilli, lactic acid, and pus cells were absent from the stomach contents. The liver seemed normal. Nothing abnormal could be felt anywhere; there was, however, slight tenderness on deep pressure in the lower epigastrium. A few days after admission the man began to show jaundice, which was slight at first, but increased rapidly and became intense in about a week. There was a very rapid increase in the signs of stagnation in the stomach, and in the enlargement of the stomach, together with the appearance of violent peristaltic movements of this viscus. The constipation was pronounced and difficult to overcome. The most striking symptom exhibited was an astonishingly rapid loss of strength and flesh. During the last two weeks of his life deep resistance, without any definite limitation of its borders, was felt in the lower epigastrium. The case was thought to be pancreatic carcinoma, and estimations of the preformed and ethereal sulphates of the urine were undertaken, and orders were also left for the feces to be sent to the laboratory. Unfortunately, these orders were not carried out. Estimation of the sulphates gave the following figures: Preformed, 2.495 grammes; ethereal, 0.085 gramme. On a second day, preformed, 2.3086 grammes; ethereal, 0.115 gramme. Further estimations could not be made, as I was obliged for several days to be out of town. The absolute values for the ethereal sulphates are very low, and the ratio between the ethereal and preformed sulphates is also in both instances decidedly below the normal, particularly in the first estimation; the normal ratio is about 1 to 10 or 1 to 12, while in this case on the first day the ratio was 1 to 29.4 and on the second day 1 to 20. The man was operated upon two days after the last estimation, and an obstruction of the duodenum and a small mass in the position of the pancreas were found. Gastro-enterostomy was done. The man did well for thirty-six hours and then collapsed and died. Only a partial post-mortem was allowed. This showed a carcinoma of the head of the pancreas completely obstructing the biliary and pancreatic ducts, the latter being absolutely closed for the distance of half an inch at its terminal portion, and behind this being dilated to a diameter of about a quarter inch. There was apparently no accessory pancreatic duct, and hence the obstruction was complete. There was no calculus. The growth had involved the intestinal wall and had caused contraction of the lumen to about the size of one's little finger. The portion of the duodenum above this was much dilated, the pylorus stretched to a diameter of an inch and a quarter, and the stomach widely dilated. There was severe gastritis, with hemorrhagic points scattered over the surface of the stomach, particularly in the pyloric region. The stomach was entirely free from carcinoma. There were a few enlarged glands in the neighborhood of the pancreas. The liver was moderately enlarged, but showed no metastases.

The second case was that of a woman, aged forty-eight years, whom I saw through the kindness of Dr. Musser and Dr. E. P. Davis. She had had some loss of general health and weight, with epigastric discomfort, and a slowly appearing and increasing jaundice, which had persisted at the time I saw her for about a month. There were no definite changes to be determined upon physical examination excepting slight enlargement of the liver, but the course of the case aroused suspicion of pancreatic carcinoma. The estimation of the urinary sulphates in this case showed on one day, preformed, 3.268 grammes; ethereal, 0.440 gramme; at a second estimation, preformed, 3.792 grammes; ethereal, 0.444 gramme. The ratio between the two was on the two days 1 to 7.4, 1 to 8.5. The absolute amount of the ethereal sulphates, therefore, was above the normal, and the ratio of the ethereal to the preformed sulphates was likewise above the normal on both days. A short time after I saw her she began to improve, and soon became entirely well and remains so now, one year after the period of her illness.

So far, then, as these two cases go they seem to indicate that a reduction of the ethereal sulphates of the urine may be a sign of value in the diagnosis of severe disease of the pancreas. The observations by themselves are, however, of little value, and the literature upon the subject is meagre. According to Oser, the first practical suggestion of this sign was in the observation by Gerhardi, in 1886, that in a case in which there was apparently obstruction high up in the intestinal tract the indican in the urine instead of being greatly increased, as is usually the case in such conditions, was almost absent. Gerhardi decided because of this that the obstruction was due to malignant disease of the pancreas involving the wall of the intestine. The post-mortem showed the correctness of his view.

Subsequently Pisenti ligated the duct in dogs and showed in two cases that this caused a marked reduction of the indican (which was estimated quantitatively). Stefanini and Biondi each reported a case of pancreatic disease, one suppurative pancreatitis, the other adenoma, in which indicanuria was absent. Schlagenhaufer, however, found the indican increased in a case of interstitial syphilitic pancreatitis. Katz, in the various experiments which he performed with Oser, usually found that lesions of the pancreas caused rather an increase of the indican than a decrease, and de Renzi could not find any distinctive change in the indican in experiments on animals. Oser decides that one is not justified in drawing any conclusions concerning the presence or absence of pancreatic disease from the observation of changes in the amount of indican. With this conclusion everyone must agree, as the indican of the urine is a very uncertain quantity and as a factor in diagnosis is of extremely limited value; but while a rough test of the amount of indican, or even its quantitative estimation, is by no means a satisfactory diagnostic measure, the accurate quantitative estimation of the total ethereal sulphates is of distinct value in many conditions. There have been, however, but few observations concerning the sulphates in the condition under discussion. The first was that of Le Nobel, in 1888, who found that in a case in which there was a glycosuria (probably maltosuria), with very fatty stools and without icterus, the ethereal sulphates were almost entirely absent from the urine, and the intestinal contents showed a practically complete absence of indol, skatol, and phenol. The salts of fatty acids were also absent from the feces, and Le Nobel believed that there was severe pancreatic disease which accounted for these changes. His diagnosis was never confirmed by post-mortem examination. A. E. Taylor showed very low values for the ethereal sulphates in a case in which the presence of cachexia and icterus, with absence of signs of gastric carcinoma or of distinctive signs of disease of the liver or bile passages, made it seem probable that there was pancreatic carcinoma. Taylor also was unable to report a post-mortem examination. Northrup and Herter described a case in which there was a mass in the region of the pancreas and the general signs of carcinoma; operation showed a growth which was apparently of the pancreas itself. Herter reports that in this case the ethereal sulphates were not reduced; they were, on the contrary, increased, and particularly in proportion to the preformed sulphates. Katz found the absolute amount of the ethereal sulphates after severe experimental lesions of the pancreas, and particularly after total or partial extirpation, variable but not greatly differing from the normal. Their ratio to the preformed sulphates was also very variable, sometimes very high and sometimes low, but never extremely low and not showing any constant tendency to be low. So far as I have been able to determine there have been no other observations concerning the test.

The summary, then, of the observations is as follows: Katz found it valueless in experimental work on dogs. Northrup and Herter found it negative in a case in which operation apparently showed a large tumor of the pancreas, while Le Nobel and Taylor found it positive in cases in which pancreatic disease may practically be accepted as present (particularly is this statement true in Le Nobel's case), and I found it positive in one case in which autopsy showed obstruction of the pancreatic duct and negative in one in which there was apparently only a protracted catarrhal jaundice. While Katz's work is important, I cannot by any means consider it so conclusive as do Katz and Oser. Observations made upon animals that have been subjected to grave operative procedures cannot alone conclusively settle questions relating to chronic diseases in man. Only a series of observations on man himself will suffice to determine the actual practical value of any test, and the very few reports of this character which I have quoted are apparently in favor of this test. Northrup and Herter's case, which gave a negative result, cannot be considered to be testimony against it, for since an autopsy was lacking it is not known whether the pancreatic duct was obstructed or not, though it probably was.

But looked at more broadly I think the test is, at best, likely to be only an inconstant aid in diagnosis and to be of real value only when positive. Normal or unduly large amounts of ethereal sulphates may certainly be conceived of as being produced even in the absence of pancreatic secretion from the intestine, since it is known that many bacteria have the power of breaking up undigested protein and may, therefore, produce indol, skatol, and their congeners without the aid of the normal digestive ferments. It is not known to what extent this may occur in the intestinal tract or what proportion of the normal amount of urinary sulphates may be furnished in this way in either diseased or normal conditions. It must be accepted as probable, however, that the amount thus produced may be sufficient to make a negative result of the test of no value as an indication of the absence of serious pancreatic disease. In the same connection it must be remembered that some pancreatic secretion may still be furnished to the intestine when there are severe inflammatory or degenerative changes in the organ, and that small amounts of the secretion may be sufficient to make the test negative. Further, it has been strongly insisted upon by Hansemann and others that new growths of an organ may to a considerable extent carry out the secretory functions of that organ, and this may be considered to be conclusively proved. Sufficient testimony of this is seen in the repeated observation of the secretion of bile by new growths of the liver; striking evidence of this is furnished in the case recorded by M. B. Schmidt, in which channels containing bile and surrounded by cells having the appearance and arrangement of liver cells were found in a sternal metastasis of a liver growth. A similar but even more remarkable observation was that of v. Eiselsberg, who noted the onset of symptoms of myxœdema after removal of the thyroid because of a malignant growth, the subsidence of the myxœdema during the growth of a metastasis, and the recurrence of the symptoms after the removal of the metastasis. The latter proved to have a structure closely resembling that of the thyroid, with acini filled with colloid material. Unless, therefore, a growth of the pancreas completely obstructs its duct the secretory function of the organ may possibly be fully carried out by the remainder of the pancreas or by the growth itself, and any tests of that function may give normal results.

On the other hand, a positive result of the test would not always be conclusive, since values for the ethereal sulphates as low as 100 mg. in the twenty-four hours have been observed by Strauss and Phillipsohn, Rovighi, Winternitz, Biernacki, Hirschler, Krauss, and others as a result of gastric hyperchlorhydria, closely restricted diet, diarrhœa, and other causes.

If, then, these causes for reduction of the ethereal sulphates are present a positive result of the test would also be of doubtful importance; hence the actual value of the test must be limited, but this does not mean that it is wholly worthless. There is scarcely a test used in clinical medicine that does not have to be carefully scrutinized in the individual case, and in so obscure a condition as pancreatic disease usually is clinically any test that promises to give aid in diagnosis is worthy of investigation. More observations must be made before definite conclusions can be reached, but it seems probable that we shall be justified in acting as follows: If the test is negative the result deserves little consideration; if, on the other hand, the ethereal sulphates are found much reduced the other factors in the case should be considered in connection with this observation. If there is diarrhœa or gastric hyperchlorhydria, or if the patient is on milk alone or any other diet which very largely reduces bacterial activity, a low ratio of the ethereal sulphates cannot be considered of great importance, nor can much stress be laid on a low absolute value of the ethereal sulphates if the values for the preformed sulphates be coincidently low. If, however, these factors be not present, and particularly if, with suspicion of pancreatic disease, factors which usually cause an increase of the ethereal sulphates be present and yet the values be found low, the test would at present appear to be of distinct practical importance in diagnosis. Constipation, gastric hypoacidity or anacidity, icterus, grave anæmia, and cachexia are all very likely to cause an increase in the relative or absolute values of the ethereal sulphates. All these factors were present in my first case, and yet the absolute value for the ethereal sulphates was low on the second day of estimation and very low on the first day, while the preformed sulphates were relatively and absolutely high. This result was considered to be a point of distinct importance in the diagnosis of this case, and I believe it would be of importance under similar circumstances. The test does not require more time or skill than one often needs in the diagnosis of new growths by the examination of sections, though it does require rather more concentration of the time expended and a little special skill in chemical work.

AS TO THE IMPORTANCE OF FATTY STOOLS IN THE DIAGNOSIS OF PANCREATIC DISEASE.

The general clinical teaching concerning this matter is an instance of the not uncommon but unfortunate persistence of a belief far beyond the time when it has been proved that it is incorrect. Since Claude Bernard first stated that he had shown that the secretion of the pancreas splits fats, produces an emulsion of the same, and causes absorption of the fats, it has been customary in works on clinical medicine and clinical diagnosis to state, with a strange degree of absoluteness, that the presence of an excessive amount of fat in the stools is strong proof of the existence of pancreatic disease. Indeed, in a number of books one finds the curiously inaccurate statement that " the presence of fat in the stools " indicates disease of the pancreas. By this the authors must, of course, mean large amounts of fat, as it is well known that every normal stool contains some fat, and the expression is, therefore, merely an inaccuracy in statement; but it is an unfortunate inaccuracy, for most students and many practitioners seem full of the belief that the presence of fat in the stools, whatever the amount, means disease of the pancreas. The question under consideration, however, really concerns the value of very fatty stools in the diagnosis of pancreatic disease.

Let me first quote the conclusions which Oser reaches after a consideration of the literature upon this point. His first conclusion is that steatorrhœa, as such, gives no justification for the recognition of disease of the pancreas. The second is that *if there is no icterus and no apparent disease of the intestine it is possible* that disturbed fat digestion is caused by pancreatic disease. Third, the probability that disease of the pancreas is present becomes more marked and can even approach certainty if, in the absence of icterus, steatorrhœa exists with other symptoms which point toward disease of the pancreas. Such symptoms are chiefly imperfect absorption of protein food, diabetes, or a tumor in the region of the pancreas. Fourth, imperfect absorption of the fat and coincident diabetes may be found in the entire absence of disease of the pancreas. Fifth, it is uncertain in how far disturbance of the normal splitting of fats may be looked upon as a pathognomonic symptom of disease of the pancreas. Fat splitting is undoubtedly a function of the pancreas, and Müller's cases indicate very positively that disturbance of fat splitting is a strong sign of pancreatic disease; but this question has not been sufficiently studied, and a positive conclusion cannot yet be reached.

In spite of the fact that Hartsen in animal experiments seemed to show that extirpation of the pancreas caused marked disturbance of the fat absorption and thereby seemed to confirm Claude Bernard's results, there is a great deal of testimony that this does not necessarily occur even under such extreme conditions, though the most important observations—those of Minkowski and Abelmann and of others who followed their methods—do seem to demonstrate positively that in animal experiments extirpation of the pancreas is followed by marked disturbance in the absorption of all fats except milk fats. It is not yet absolutely pròved, however, that even extirpation of the pancreas has as a necessary result severe disturbance of fat absorption. The chief basis of the rather absolute teaching of clinicians seems to be the fairly frequent observation of the presence of fatty stools in cases which are, clinically, believed to be disease of the pancreas. The diagnosis of disease of the pancreas is, however, so insecure that it is surprising that clinicians have been so wedded to mere isolated observations without engaging in more careful study of the literature concerning experimental work and that concerning the conditions found in human subjects who showed other affections than disease of the pancreas. It is now fourteen years since a very important contribution by F. Müller showed very conclusively that icterus of itself, unassociated with pancreatic disease but, of course, associated with absence of bile from the intestine, was accompanied by the passage of extremely fatty stools. In spite of the long period since this work was published, it is rather astonishing to see perpetuated in many of the most important works on general medicine and clinical diagnosis as well as in many special treatises on diseases of the pancreas the unvarnished statement that fatty stools are indicative of pancreatic disease. The most important fact which shows this teaching to be erroneous is that Müller's work and that of other observers, Walters especially, has demonstrated definitely that fatty stools can be seen in most cases of icterus in which the pancreas is entirely uninvolved. This had also been thoroughly demonstrated years before in experimental work on animals. But it must also be remembered that Müller showed, and his work has been confirmed by other observers, that severe disease of the intestine causes such pronounced disturbance of fat absorption as to give rise to the passage of stools that are very largely composed of fat.

The one observation which I have to report in this connection relates to the importance of icterus in the production of fatty stools. The second case to which I referred in discussing the sulphates was put upon a diet consisting solely of milk. The fat of the milk was estimated daily by the Leffmann-Beam method, the stools were marked off by charcoal, and three days' stools were collected, a strong solution of corrosive sublimate being added to prevent continued bacterial activity. The stools were evaporated to dryness. As they came to me the stools were completely acholic in appearance; they had a pale, grayish-yellow color, appeared to be composed chiefly of fat, and were extremely pasty and oily in consistency. After evaporation to dryness it was evident that they were composed almost entirely of fat, for even when the water was completely driven off moderate heating on a water-bath caused the whole mass to become completely fluid and to assume the appearance of oil. Upon cooling the stools became solid, but even when cold the consistency was much like that of a mass of pure fat. The total amount of dried feces in the three days was 184.69 grammes. Of this 154.18 grammes were shown by complete ether extraction in the Soxhlet apparatus to consist of fat. Hence of the total amount of dried feces 83.48 per cent. was fat. The patient during the three days ingested 250.8 grammes of fat, and the total amount of fat in the feces was 154.18 grammes. She absorbed, therefore, only 61.6 per cent. of the fat ingested, while normally as much as 90 per cent. is usually absorbed. This patient, as will be remembered, became entirely well soon after this observation was made, and it may therefore be stated, I think, that there was no pancreatic disease. There was, however, pronounced icterus, and it is almost unquestionable that the icterus alone caused the marked disturbance of fat absorption. This is only a single contribution to the work to which I particularly referred—that of Müller, in which he showed clearly that icterus causes profound disturbance of absorption of fats—but it serves to add emphasis to the statement quoted that poor fat absorption is of itself of no importance in the diagnosis of pancreatic disease if icterus is present; and in carcinoma—the most common disease of the pancreas—icterus is so frequently present as to make such a statement one of great importance.

The last of Oser's conclusions, to which I referred earlier, relates to the observation made by Müller that while the fat absorption is greatly disturbed by absence of bile from the intestine, the splitting of the fats is normal in this condition, but is much reduced in pancreatic disease. As stated by Oser, there have been few studies of this question excepting those made by Müller himself. v. Noorden obtained results similar to Müller's in two cases of pancreatic disease. Northrup and Herter, in the case which has previously been referred to, investigated the splitting of the fats with negative results, the fat digestion being normal; but, as they state, negative observations do not invalidate Müller's teaching. It is quite possible that the intestinal bacteria may exercise sufficient fat-splitting action to make a negative result in such an investigation of no value. It is also quite possible, I think, as I said before in speaking of the sulphates, that the pancreatic duct at the time of examination may have been open or only incompletely closed; pancreatic secretion may have been produced to some extent, and the secretion may have partly or wholly escaped into the intestine, thus making the result negative.

It seems probable that a negative result of this test also would not be of much value, for such a result would be subject to about the same considerations that I have suggested in speaking of the ethereal sulphates. A positive result, however, so far as our knowledge now goes, would seem to be an indication of pancreatic disease if diarrhœa were absent, for I am not aware that marked disturbance of the fat-splitting action has been observed in any case in which it was known that pancreatic disease was absent, excepting when severe intestinal disturbance was evidently present.

In the case of prolonged catarrhal jaundice in which I studied the fat absorption I also investigated the amount of fat splitting that had taken place; 78 per cent. of the large amount of fats that was present in the feces was fatty acids and soaps, only 22 per cent. being found as neutral fat. These conditions are entirely normal, and hence the case also serves to add some weight to Müller's statement that icterus, while largely interfering with fat absorption, does not disturb the splitting of the fats. In the case of pancreatic carcinoma a study of the digestion of the fats would have been more directly of diagnostic interest. Unfortunately, such a study could not be carried out, because the stools were not preserved owing to confusion resulting from a change of ward nurses.

LITERATURE.

Oser. Die Erkrankungen des Pankreas. Nothnagel's spec. Pathol. u. Therap., Bd. xviii., Abtheil. II., p. 99.
Gerhardi. Virchow's Archiv, 1886, S. 303.
Pisenti. Arch. per le sc. Med., 1888, p. 87.
Stefanini. Gaz. degli osped., 1896, p. 848.
Biondi. Riforma med., 1896, vol. ii., No. 9, p. 97.
Schlagenhaufer. Arch. f. Dermatol. u. Syph., 1895, Bd. xxxi. S. 43.
Le Nobel. Deutsch. Archiv f. klin. Med., Bd. xliii. S. 285.
A. E. Taylor. Transactions Philadelphia Pathological Society, vol. ii., new series.
Northrup and Herter. AMERICAN JOURNAL OF THE MEDICAL SCIENCES, February, 1899.
M. B. Schmidt. Virchow's Archiv, Bd. clviii.
Strauss and Phillippsohn. Zeitsch. f. kl. Med , Bd. xl., Hefte 5 and 6.
Hoppe-Seyler. Zeitsch. f. physiol. Chemie, Bd. xii.
Rovighi. Zeitsch. f. physiol. Chemie, Bd. xvii.
Winternitz. Zeitsch. f. physiol. Chemie, Bd. xvi.
Biernacki. Zeitsch. f. physiol. Chemie, Bd. xvii and xix.
Hirschler. Zeitsch. f. physiol. Chemie, Bd. x.
Krauss. Zeitsch. f. physiol. Chemie, Bd. xviii.
Müller. Zeitsch. f. klin. Med., 1887, Bd. xii. p. 45.
Walter. Abstract in Maly's Jahresbericht, 1888, Bd. xvii. p. 27.
v. Noorden. Berl. klin. Woch., 1900, S. 1022.
Minkowski and Abelmann. Berl. klin. Woch., 1890, No. 15. Dissertation by Abelmann, 1890 and Maly's Jahresbericht, 1890, Bd. xx. p. 44.

PREMATURE INFANTS.

BY VANDERPOEL ADRIANCE, M.D.,
OF NEW YORK.

I HAVE selected the subject of premature infants because it has been inadvertently neglected. The theme is far from hackneyed; and as I have had unusual facilities for observing this class of patients at the Nursery and Child's Hospital of this city, it is hoped the subject may be of interest. Records of forty cases are in my possession, of which a large majority have come under my observation clinically or on the autopsy table.

On examining a premature infant we are impressed with its general diminutive characteristics, with which the excessively developed head ill corresponds. The skin is a raw, cinnamon-red, and presents lanugo in proportion to the period of prematurity, while the lack of subcutaneous fat gives the skin a wrinkled appearance and the face an expression of senility. The greater the period of prematurity the more marked the torpor and inactivity of the child. The limbs evince little motion, and the occasional feeble whine contrasts strongly with the cry